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Intramyocellular Lipids and Insulin Sensitivity: Does Size Really Matter?

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Storage of free fatty acids as triacylglycerol in lipid droplets in nonadipose tissue, such as skeletal muscle, is considered "normal" physiology. However, in the insulin resistant state, the level of intramyocellular lipid (IMCL)[1] is increased and correlates closely and inversely with insulin sensitivity (IS) (1). Weight loss induced by caloric restriction improves IS and decreases IMCL content. These findings suggest that excessive IMCL storage is associated with "pathophysiology." On the other hand, high levels of IMCL are also observed in insulin-sensitive, endurance trained athletes (2). Exercise training, known to improve IS, increases IMCL within 2 weeks in previously untrained subjects (3). Hence, the relationship between IMCL and IS is unlikely to be causal.

In overweight subjects, caloric restriction combined with exercise training (i.e., conditions with opposite effects on IMCL) is advocated by the NIH and World Health Organization to improve health and IS. In this issue of *Obesity Research*, He et al. report on the combined effect of weight loss by caloric restriction and a 16-week exercise training program on IS and IMCL content (4). The investigators found that IS was improved, but IMCL content was unaffected, suggesting no involvement of IMCL in IS. Remarkably, however, IMCL was dispersed into smaller droplets after intervention and the decrement in droplet size correlated highly with improved IS.

Determination of change in size of IMCL by light microscopy is not without pitfalls. It requires very high-quality lenses and approaches the limitations in optical resolution of the most routinely used microscopes and cameras. In addition, droplet size may vary with the fixative used (5). Using external calibration standards, He et al. elegantly overcame these drawbacks, providing us with the novel and invigorating observation that size of IMCL is related to IS. However, we are left with the following question: what physiological mechanism underlies this observation?

Information on proteins controlling the storage and release of fatty acids in lipid droplets in skeletal muscle is fragmentary, but much can be learned from lipid droplets within adipocytes. In adipocytes, the phospholipid monolayer surrounding the droplet is coated with proteins controlling droplet size [e.g., members of the PAT (Perilipin A, Adipocyte differentiation-related protein, and Tail-interacting protein 47) protein family (6)]. Of the PAT proteins regulating lipid droplet size and lipase accessibility known to date, only adipocyte differentiation-related protein and Tail-interacting protein 47 are expressed in muscle and are, therefore, putative targets to manipulate lipid droplet size, thus modulating lipase accessibility.

How can droplet size affect insulin sensitivity? As a consequence of the smaller droplet size, the surface-to-volume ratio of the droplets increases. Thus, the density of PAT proteins relative to the triacylglycerol content in the droplet increases and access of cytosolic lipases involved in hydrolysis of triacylglycerol within the lipid droplet improves (7). Incomplete hydrolysis of triacylglycerol in lipid droplets, which is more likely in larger droplets due to reduced accessibility for lipases, will result in increased diacylglycerol (DAG) levels. Recent data indicate that DAG, rather than IMCL per se, impedes insulin signalling by serine phosphorylation of insulin receptor substrate 1, thereby reducing insulin sensitivity (8).

Although reduced droplet size may improve lipase accessibility, the fatty acids released must be diverted rapidly toward oxidation to achieve complete hydrolysis of IMCL. Both the increased succinate dehydrogenase activity and mitochondrial content that He et al. report contribute to improved fat oxidative capacity. Hence, the improved IS reported may originate from, or require, at least two interrelated adaptive responses: 1) dispersion of IMCL in smaller droplets, permitting improved accessibility and interaction of the lipases with the triacylglycerols within the droplets and, thereby, possibly reducing DAG levels; and 2) an improved capacity to divert the fatty acids released after hydrolysis of the lipid droplets toward oxidation, preventing

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[1] Nonstandard abbreviations: IMCL, intramyocellular lipid; IS, insulin sensitivity; DAG, diacylglycerol.

these fatty acids from lipid peroxidation, thus reducing lipotoxicity.

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